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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,299	08/25/2006	Orit Kollet	30694/41506	2069
4743 7590 06/01/2010 MARSHALL, GERSTEIN & BORUN LLP 233 SOUTH WACKER DRIVE 6300 WILLIS TOWER CHICAGO, IL 60606-6357			EXAMINER SHEN, WU CHENG WINSTON	
			ART UNIT 1632	PAPER NUMBER
			MAIL DATE 06/01/2010	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action
Before the Filing of an Appeal Brief

Application No.

10/552,299

Applicant(s)

KOLLET ET AL.

Examiner

WU-CHENG Winston SHEN

Art Unit

1632

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 17 March 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
(b) ☐ They raise the issue of new matter (see NOTE below);
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
The status of the claim(s) is (or will be) as follows:
Claim(s) allowed: _____.
Claim(s) objected to: _____.
Claim(s) rejected: 30-36, 38 and 39.
Claim(s) withdrawn from consideration: 1-29, 37 and 40-62.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____.
13. ☐ Other: _____.

Continuation of 11, does NOT place the application in condition for allowance because:

Applicant's arguments have failed to overcome the rejection of claims 30-36, 38, and 39 under 35 U.S.C. 103(a) as being unpatentable over Kollet et al. (Kollet et al., Rapid and efficient homing of human CD34(+) CD38/low CXCR4(+) stem and progenitor cells to the bone marrow and spleen of NOD/SCID and NOD/SCID/B2m(null) mice, *Blood* 97(10):3283-91, 2001; this reference is listed as reference C35 in the IDS filed by Applicant on 01/29/2007) in view of Heissig et al. (Heissig et al. Recruitment of stem and progenitor cells from the bone marrow niche requires MMP-9 mediated release of kit-ligand, *Cell* 109(5):625-37, 2002), Togawa et al. (Togawa et al., Highly activated matrix metalloproteinase-2 secreted from clones of metastatic lung nodules of nude mice injected with human fibrosarcoma HT1080, *Cancer Lett.* 146(1):25-33, 1999), Rafii et al. (US 2004/0071687, publication date 04/15/2004, filed on 05/28/2003, provisional application 60/383,658 filed on 05/28/2002), and Sadatmansoori et al. (Sadatmansoori et al. Construction, Expression, and Characterization of a Baculovirally Expressed Catalytic Domain of Human Matrix Metalloproteinase-9, *Protein Expr Purif.* 23(3):447-52, 2001). Applicant's arguments filed 03/17/2010 have been fully considered and they are NOT persuasive. Previous rejection is maintained for the reasons of record advanced on pages 4-14 of the office action mailed on 01/20/2010.

Applicant argues that the Office also mischaracterized the teachings of Rafii in stating that Rafii "teaches that MMP-9 promotes release of stem cell active cytokines (e.g. SDF-1), thereby promoting expansion of quiescent stem cells, and this novel concept lays the foundation of developing strategies where activation of proteases such as MMP-9 may act as molecular switches to expand a large population of stem cells that may ultimately be used for organ-regeneration and tissue vascularization." See Office Action, p. 11. This represents an exact quote of paragraph 114 of Rafii except for the addition of "(e.g. SDF-1)" by the Office. In fact, nowhere in Rafii is there a disclosure or suggestion of SDF-1 as a stem cell-active cytokine whose release is promoted by MMP-9 (See page 11 of Applicant's remarks filed on 03/17/2010).

Applicant states that the Office goes on to use the above-quoted language as a basis to combine Heissig and Rafii to yield a combined teaching of a "functional positive feedback loop of increased SDF-1/CXCR4 interaction and increased MMP-9 expression in regulation of hematopoietic stem cells (HSCs) mobilization and differentiation." Id. No such positive feedback loop is disclosed or suggested by Rafii and/or Heissig because Rafii does not teach that MMP-9 promotes release of SDF-1. Both Rafii and Heissig teach that increased levels of SDF-1 lead to up-regulation of MMP-9. See Rafii, paragraph 199; Heissig, p. 630, left column, last paragraph. Applicant states that the positive feedback loop proposed by the Office would lead to runaway expression of SDF-1 and MMP-9. In other words, an increase in MMP-9 would lead to an increase in SDF-1, which would lead to a further increase in MMP-9, in an ever-escalating spiral of mutually increased expression. None of the references cited by the examiner, alone or in combination, teach or suggest the positive feedback loop proposed by the Office. Thus, the Office improperly relied upon a flawed understanding of the cited references as a basis for combining the teachings of Rafii and Heissig to arrive at the conclusion that the claims would have been obvious.

Applicant states that to support a conclusion that a claim would have been obvious, the Office must show that all of the claimed elements were known or suggested in the cited references or in the state of the art, and that one of skill in the art would have combined the elements with no change in their respective functions. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007). In no instance does Rafii or Heissig, alone or in combination, disclose or suggest that MMP-9 promotes release of SDF-1. Applicant states that the office cited no reason to combine Rafii and Heissig in order to arrive at the use of matrix metalloproteinase MMP-9 to induce expression of SDF-1, in turn leading to increased CXCR4 expression and HSC homing to BM. The cited references do not disclose, or even suggest, that exposing stem cells to an exogenous matrix metalloproteinase allows one to isolate cells having increased CXCR4 levels compared to stem cells not exposed to the matrix metalloproteinase, as required by claim 30. Applicant states that, moreover, the remaining cited references, Togawa and Sadatmansoori, do not remedy any of these defects and the Office has not contended otherwise. Thus, the Office has not provided a reason for combining the cited references and has not established that one of skill would have a reasonable expectation of successfully arriving at the claimed subject matter. Accordingly, the Office has not established a prima facie basis for rejecting any of the claims as obvious under 35 U.S.C. § 103(a) over Kollet in view of Heissig, Rafii, Togawa, and Sadatmansoori, and the rejection should be withdrawn.

In response, Applicant is reminded that the rejection of the record is a 103 rejection, not a 102 rejection. It is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

It is noted that SDF-1 is a cytokine taught by primary reference Kollet et al. (See page 7 of the office action mailed on 01/20/2010) and by second reference Heissig et al. in the context of regulating MMP-9 function in the recruitment of stem and progenitor cells from the bone marrow niche (See page 9 of the office action mailed on 01/20/2010). Furthermore, contrary to Applicant's arguments, SDF-1 is also taught by the fourth reference Rafii et al. (see line 18, page 11 of the office action mailed on 01/20/2010). Accordingly, as documented on page 11 of the office action mailed on 01/20/2010, with regard to the limitation "wherein said exposing said stem cells to said exogenous matrix metalloproteinase or said active portion thereof, is effected by: (i) expressing a polynucleotide encoding said matrix metalloproteinase or said active portion thereof in said stem cells, as recited in claim 38, Rafii et al. (US 2004/0071687) teaches that MMP-9 promotes release of stem cell active cytokines (e.g. SDF-1), thereby promoting expansion of quiescent stem cells," and this "novel concept lays" the foundation of developing strategies where activation of proteases such as MMP-9 may act as molecular switches to expand a large population of stem cells" that may ultimately be used for organ-regeneration and tissue vascularization (See paragraph [0114], US 2004/0071687).

Applicant's arguments regarding "an increase in MMP-9 would lead to an increase in SDF-1, which would lead to a further increase in MMP-9, in an ever-escalating spiral of mutually increased expression" have been fully considered and found NOT persuasive. The Examiner notes Applicant's arguments appear to describe a "completely close and exclusive functional positive feedback loop

between increased SDF-1/CXCR4 interaction and increased MMP-9 expression" in an assumed context complete absence of any regulation for hematopoietic stem cells (HSCs) mobilization and differentiation. This argument is certainly inconsistent with the teachings by Heissig et al. and Rafii et al. The Examiner maintains the position that, as documented in the maintained rejection, the combined teachings of Heissig et al. and Rafii et al. discloses a functional positive feedback of increased SDF-1/CXCR4 interaction and increased MMP-9 expression in regulation of hematopoietic stem cells (HSCs) mobilization and differentiation. Rafii et al. (US 2004/0071687) further teaches DNA constructs, adenoviral vector, expressing various cytokines, including AdSDF-1 and AdVEGF (See for instance, paragraph [0165], US 2004/0071687). Furthermore, Sadatmansoori et al. teaches DNA construction, baculovirus expression, and partial characterization of a minienzyme form of the human matrix Construction, Expression, and Characterization of a Baculovirally Expressed Catalytic Domain of Human Matrix Metalloproteinase-9, Protein Expr Purif. 23(3):447-52, 2001). It is worth noting that up-regulation in MMP-9 expression resulting from the induction of SDF-1 taught by Heissig (See page 9 of the Final office action mailed on 01/20/2010) does NOT in any way teaches that the "induction" lasts forever and eventually results in "an ever-escalating spiral of mutually increased expression" as Applicant argues. In other words, the positive correlation between induction of SDF-1 and increased MMP-9 expression is a regulated process as clearly taught by Heissig et al.

With regard to the asserted requirement for teaching/suggestion/motivation, the Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in KSR International Co. v. Teleflex, Inc. that forecloses the argument that a specific teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) (available at <http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf>). The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in KSR International Co. v. Teleflex, Inc., the suggestion and motivation to combine Kollet et al. in view of Heissig et al., Togawa et al., Rafii et al., and Sadatmansoori et al. have been clearly set forth on pages 4-14 of the office action mailed on 01/20/2010.

/Wu-Cheng Winston Shen/
Primary Examiner, Art Unit 1632